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# Epidemic *Pseudomonas aeruginosa* Serotype O16 Bacteremia in Hematology-Oncology Patients

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**From 1 August 1978 through 31 December 1982, 98 hematology-oncology patients had positive cultures for *Pseudomonas aeruginosa* serotype O16; 22 of these patients developed bacteremia, and this bacteremia was associated with the occurrence of extensive perineal cellulitis in 10 patients (45.5%). Seventeen bacteremic patients died. The epidemic strain differed from other *P. aeruginosa* organisms isolated at the hospital by its resistance to all antibiotics available at that time (ticarcillin, piperacillin, azlocillin, tobramycin, ceftizoxime, ceftriaxone, moxalactam, ceftazidime, and fosfomycin). Univariate analysis showed the following factors to be significantly associated with *P. aeruginosa* O16 bacteremia: the severity of granulocytopenia at the time of the bacteremia, more days with fever, the administration of ticarcillin or an aminoglycoside, the receipt of a greater number of antimicrobial agents for a longer period of time before documentation of the bacteremia, and the occurrence of cellulitis. Logistic regression analysis showed that duration of fever, duration of bacteremia, and the number of antimicrobial agents administered before documentation of the bacteremia were the best predictors of *P. aeruginosa* O16 bacteremia. In a prospective study of the acquisition of *P. aeruginosa* by hematology-oncology patients, 1,149 specimens (throat and rectal swabs) from 270 patients and 201 specimens from their washbasin drains were collected. On only three occasions was the epidemic strain isolated from both the patient and his or her washbasin, but in each case the colonization of the patient preceded the isolation of the strain from the washbasin. The transmission of any *P. aeruginosa* organism from washbasin drain to patient could not be documented. Contact isolation precautions from the Centers for Disease Control were used for all hematology-oncology patients colonized or infected with *P. aeruginosa* after 7 January 1983. No case of *P. aeruginosa* O16 bacteremia has occurred at Hotel Dieu since July 1984.**

*Pseudomonas aeruginosa* is frequently responsible for infections in cancer patients, in particular leukemic patients with granulocytopenia following chemotherapy. These infections are usually endemic and involve several different serotypes. In this report we describe an outbreak of infections caused by *P. aeruginosa* serotype O16; this multiply resistant strain was responsible for 22 cases of bacteremia from August 1978 through December 1982, with a mortality rate of 77%. This epidemic had several remarkable features: (i) perineal cellulitis developed in 45.5% of bacteriemic patients; (ii) 1 case patient had positive urine cultures during a 33-month period and 11 other patients were colonized at various sites and represented the reservoir for the epidemic strain; and (iii) the presence of the epidemic strain in the hospital environment was the consequence and not the cause of infection or colonization in hematology patients.

## MATERIALS AND METHODS

**Background.** Since 1974, we have studied the ecology of *P. aeruginosa* at Hotel Dieu and serotyped all *P. aeruginosa* isolates; this enabled the microbiology laboratory to detect any variation in the isolation rate of the different *P. aeruginosa* serotypes.

From 1 November through 31 December 1982, three patients hospitalized in a hematology-oncology (HO) service developed bacteremia caused by *P. aeruginosa* serotype O16; all three patients died.

Bacteriologic investigation of the environment found *P. aeruginosa* serotype O16 in the washbasin drains in the rooms of several patients despite biweekly disinfection with hypochlorite.

An epidemiologic investigation was initiated to determine the cause of this epidemic and to formulate recommendations to prevent additional cases.

The HO service consisted of four subunits: A, 9 rooms (13 beds); G, 7 rooms (12 beds); M, 11 rooms (23 beds); and a sterile area of 2 rooms with laminar airflow filters. Each room had its own toilets and washroom.

The microbiology laboratory at the hospital processed all blood cultures by using aerobic (ventilated) and anaerobic bottles (Institut Pasteur Production, Paris, France). The oxidase-positive, aerobic gram-negative bacilli were identified with a *Pseudomonas* sp. identification test kit (Institut Pasteur Production).

*P. aeruginosa* serotypes were routinely determined by the International Antigenic Typing System by using 17 type-specific rabbit antiserums (Institut Pasteur Production). Antimicrobial susceptibility was determined by the agar disk method, and MICs were determined by serial dilution on agar medium.

**Epidemiologic investigation. (i) Case definition.** A case patient was defined as any HO patient with a blood culture positive for *P. aeruginosa* serotype O16 from 1 January 1975 through 31 December 1982.

**(ii) Case ascertainment.** Microbiology records were reviewed from 1 January 1975 through 31 December 1982.

**(iii) Review of case patients.** We reviewed the medical records of all case patients and abstracted information on age, sex, nature and stage of the underlying disease, interval between the diagnosis of the malignancy and the onset of the

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bacteremia, the number of hospitalizations in the HO service before the bacteremia developed, the number of days with fever before the first positive blood culture, the number of antimicrobial agents administered before the onset of bacteremia, the granulocyte count at the time of the bacteremia, the date and nature of all specimens positive for *P. aeruginosa* serotype O16, and the outcome of the infection.

**(iv) Case-control study.** To assess the risk factors associated with *P. aeruginosa* serotype O16 bacteremia, we compared 21 case patients and 17 HO patients in whom a bacteremia caused by a *P. aeruginosa* isolate of a serotype other than O16 developed. The charts of controls were reviewed for the same details as were those of case patients.

**(v) Statistical methods.** Student's *t* test and Fisher's exact test were used to test for significance of associations. BMDP statistical software (Department of Biomathematics, University of California, Los Angeles) was used for stepwise logistic regression analysis. All potential risk factors significantly associated with *P. aeruginosa* serotype O16 bacteremia in the univariate analysis were entered in the model.

**(vi) Prospective study of *P. aeruginosa* acquisition by patients hospitalized in HO service.** Throat and rectal swabs were taken systematically from all HO patients on admission and at intervals of 1 week until their discharge from the HO service. Swab samples were also taken once a week from the washbasin drain of the patients' rooms. All specimens were inoculated on cetrimide agar plates (Institut Pasteur Production) and incubated for 48 h at 37°C.

## RESULTS

Review of the microbiology records showed that from 1 August 1978 through 31 December 1982, 98 patients had cultures positive for *P. aeruginosa* serotype O16; 22 (22.4%) of these patients developed serotype O16 *P. aeruginosa* bacteremia. The mortality rate was 77% (17 of 22). Bacteremia was associated with the occurrence of extensive perineal cellulitis in 10 patients (45.5%); the site of the cellulitis was the anus in 5 case patients, the vulva in 3 case patients, and the scrotum in the remaining 2 case patients. Two patients developed two episodes of bacteremia caused by serotype O16 *P. aeruginosa*, separated by intervals of 4 and 16 months; each time the bacteremia followed chemotherapy, and the onset of the bacteremia was coincident with granulocytopenia (<100/mm$^3$).

The epidemic strain differed from other *P. aeruginosa* organisms isolated at the hospital by its resistance to all antibiotics available at that time; the strain was found to be susceptible to either antibiotics with low in vivo activity, such as colimycin (MIC, 1 μg/ml) and amikacin (MIC, 4 μg/ml), or to antibiotics not readily available, such as aztreonam (MIC, 4 μg/ml), thienamycin (MIC, 2 μg/ml), or pefloxacin (MIC, 2 μg/ml).

**Descriptive epidemiology.** The review of the microbiology records showed that although 12 HO patients had been colonized with the epidemic strain for 1 to 33 months (mean, 5.5 ± 8.6 months), only 4 (33%) of them developed *P. aeruginosa* serotype O16 bacteremia. Those colonized patients who did not develop bacteremia did not receive intensive chemotherapy when they were colonized. The sites of colonization were: gastrointestinal tract, 8 (67%); urinary tract, 6 (50%); skin (axillae and groin), 4 (33%); respiratory tract, 3 (25%); and genitals, 3 (25%). Six (50%) patients were colonized on multiple sites. Analysis of patients whose cultures were positive for *P. aeruginosa* O16 by date of admission and room location did not show any association between the room occupied and colonization or infection in HO patients. Colonized or infected patients had occupied 93% of the rooms (25 of 27) in the HO service, and on only six occasions had two colonized patients shared the same room. In one instance, the transfer of a colonized patient from subunit G to subunit A resulted in transmission of the epidemic strain to seven additional patients (26 positive cultures). The epidemic strain had never been isolated in that subunit during the previous 3 months. The epidemic strain was isolated during the same period from five washbasin drains in subunits G and M, while this strain was not isolated from any patient. In addition, the epidemic

TABLE 1. Assessment of risk factors for *P. aeruginosa* serotype O16 bacteremia in HO patients 1 August 1978 to 31 December 1982: host factors and hospitalizations

| Potential risk factor[a] | Case patients (*n* = 21) | Controls (*n* = 17) |
|---|---|---|
| Mean age (yr) | 45.4 ± 21 | 49.6 ± 18 |
| Sex (male) | 9 (43) | 12 (71) |
| Leukemia | | |
| Acute myelogenous | 10 (48) | 6 (35) |
| Acute nonlymphoblastic | 1 (5) | 1 (6) |
| Acute lymphocytic | 2 (10) | 2 (12) |
| Chronic myelogenous | 1 (5) | 4 (24) |
| Lymphoma | 1 (5) | 1 (6) |
| Hodgkin | 0 | 1 (6) |
| Myeloma | 0 | 1 (6) |
| Hematosarcoma | 1 (5) | |
| Aplasia | 3 (14) | 0 |
| Refractory anemia | 1 (5) | 1 (6) |
| Interval diagnosis cancer bacteremia, mean (mo) | 22.7 ± 40 | 21.5 ± 23 |
| Hospitalization in unit: | | |
| M | 14 (67) | 9 (53) |
| G | 7 (33) | 6 (35) |
| A | 7 (33) | 7 (41) |
| No. of hospitalizations in unit (mean): | | |
| M | 2.9 ± 3 | 4.3 ± 3 |
| G | 2.1 ± 2 | 3.5 ± 3 |
| A | 1.7 ± 2 | 1.7 ± 1 |

[a] Unless otherwise specified, all values are given as number (percent) of patients.

TABLE 2. Assessment of risk factors: colonization[a] and portal of entry

| Potential risk factor | No. (%) | |
|---|---|---|
| | Case patients (*n* = 21) | Controls (*n* = 17) |
| *P. aeruginosa* colonization | 4 (19) | 7 (41) |
| Site of colonization | | |
| GI tract[b] | 2 (10) | 4 (24) |
| Respiratory tract | 1 (5) | 2 (12) |
| Urinary tract | 0 | 2 (12) |
| Skin | 1 (5) | 1 (6) |
| Genitals | 0 | 1 (6) |
| Portal of entry | | |
| GI tract | 7 (32) | 9 (53) |
| Skin | 3 (14) | 0 |
| Urinary tract | 3 (14) | 2 (12) |
| Respiratory tract | 2 (9) | 2 (12) |
| Unknown | 7 (32) | 4 (24) |

[a] Duration of colonization (mean days ± standard deviation): case patients, 38.5 ± 14; controls, 7.9 ± 4; $P = 0.008$.
[b] GI, Gastrointestinal.

TABLE 3. Assessment of risk factors: chemotherapies and neutropenia

| Potential risk factor[a] | Case patients ($n$ = 21) | Controls ($n$ = 17) | $P$ |
|---|---|---|---|
| Receipt of chemotherapy before bacteremia | 18 (86) | 14 (82) | NS[b] |
| Adriamycin | 3 (14) | 3 (18) | NS |
| Vincristine | 7 (33) | 6 (35) | NS |
| Aracytosine | 9 (43) | 7 (41) | NS |
| Steroids | 7 (33) | 4 (24) | NS |
| Daunorubicin | 3 (14) | 2 (12) | NS |
| Amsacrine | 1 (5) | 3 (18) | NS |
| Vinblastine | 0 | 2 (12) | NS |
| Cyclophosphamide | 0 | 2 (12) | NS |
| No. of chemotherapy treatments before bacteremia (mean) | 2.1 ± 3 | 2.4 ± 2 | NS |
| Polymorphonuclear leukocytes at the time of bacteremia (/mm$^3$)[c] | | | |
| 0 | 4 (19) | 2 (12) | NS |
| 0–100 | 13 (62) | 6 (35) | NS |
| 100–500 | 4 (19) | 5 (29) | NS |
| 500–1,000 | 0 | 1 (6) | NS |
| >1,000 | 0 | 3 (18) | NS |
| Mean no. of days with <100 polymorphonuclear leukocytes/mm$^3$ | 14.7 ± 16 | 5 ± 6 | 0.002 |

[a] Unless otherwise specified, all values are given as number (percent) of patients.
[b] NS, Not significant.
[c] Mean values: Case patients, 109 ± 156/mm$^3$; controls, 887 ± 1, 665/mm$^3$; $P$ = 0.03.

strain was never isolated from patients hospitalized in the sterile area.

**Analytic epidemiology.** To assess the risk factors for serotype O16 *P. aeruginosa* bacteremia, 17 HO patients who had bacteremia caused by another *P. aeruginosa* serotype (serotype O1, 3; O2, 2; O3, 2; O5, 3; O6, 4; O11, 2; nontypeable, 1) during the epidemic period were compared with the 21 case patients (the medical record of one case patient was not available for review). No significant differences were found concerning age, sex, nature of the underlying disease, the interval between the diagnosis of the hematologic disease and the onset of the bacteremia, the number of hospitalizations before the bacteremia developed (Table 1), and the portal of entry of the bacteremia (Table 2). Several characteristics were significantly associated with the case patients: severity of granulocytopenia at the time of the bacteremia, a longer duration of neutropenia before bacteremia (Table 3), more days with fever, the occurrence of cellulitis, the receipt of a greater number of antimicrobial agents for a longer period of time, and the receipt of two antimicrobial agents, ticarcillin and an aminoglycoside (Table 4). Although the numbers of patients colonized with *P. aeruginosa* before the onset of the bacteremia were similar in both groups, the duration of the colonization was significantly longer in case patients (Table 2). The overall mortality rate was significantly higher in case patients (77 versus 41%; $P$ = 0.04; odds ratio = 4.9; 95% confidence interval, 1.01 to 25). The mortality rate directly attributable to the bacteremia (septic shock or death within a week after the onset of the bacteremia) was slightly higher in case patients (57% [12 of 21] versus 41% [7 of 17]; $P$ = 0.5).

Logistic regression analysis showed that duration of fever ($P$ = 0.0001; odds ratio = 4.6), duration of neutropenia ($P$ = 0.007; odds ratio = 4.4), and the number of antimicrobial agents administered before the bacteremia developed ($P$ = 0.03; odds ratio = 3.1) were independent risk factors and the best predictors of *P. aeruginosa* serotype O16 bacteremia.

**Prospective study of *P. aeruginosa* acquisition by HO patients.** We collected 1,149 specimens (throat and rectal swabs) from 270 patients and 201 specimens from washbasin drains. Eight patients (3%) acquired *P. aeruginosa* during their hospitalization; four patients were already colonized at the time of admission. The epidemic strain accounted for 37.5% of *P. aeruginosa* organisms isolated from patients and for 21.3% of the strains isolated from washbasins. Serotype O6 was the most common *P. aeruginosa* serotype isolated from washbasins and was, with the epidemic strain, the most common serotype isolated from patients (Fig. 1). On only three occasions was the epidemic strain isolated from both the patient and his or her washbasin, but in each of these

TABLE 4. Assessment of risk factors: fever and antimicrobial agents

| Potential risk factor[a] | Case patients ($n$ = 21) | Controls ($n$ = 17) | Odds ratio | 95% Confidence interval | $P$ |
|---|---|---|---|---|---|
| No. of days with fever before bacteremia | 17.7 ± 14 | 7.6 ± 5 | | | 0.001 |
| No. of antibiotics received before bacteremia (mean) | 5.4 ± 2.8 | 2.9 ± 2.2 | | | 0.006 |
| Duration of antimicrobial therapy, mean (days) | 22.8 ± 20 | 10.2 ± 9 | | | 0.01 |
| Antimicrobial agent | | | | | |
| Cefotaxime | 10 (48) | 5 (29) | | | NS[b] |
| Ampicillin | 5 (24) | 3 (18) | | | NS |
| Colimycin | 4 (19) | 1 (6) | | | NS |
| Aminoglycosides | 21 (100) | 11 (65) | Und[c] | 1.8–Und | 0.004 |
| Trimethoprim-sulfamethoxazole | 5 (24) | 4 (24) | | | NS |
| Vancomycin | 4 (19) | 0 | | | NS |
| Ticarcillin | 11 (52) | 3 (18) | 5.1 | 0.96–34 | 0.03 |
| Cellulitis | 12 (57) | 0 | Und | 3.9–Und | 0.0006 |
| Other positive blood culture | 8 (38) | 5 (29) | | | NS |
| *Escherichia coli* | 4 (19) | 3 (18) | | | NS |
| *Klebsiella oxytoca* | 1 (5) | 0 | | | NS |
| *Staphylococcus aureus* | 1 (5) | 2 (12) | | | NS |
| *Staphylococcus epidermidis* | 1 (5) | 0 | | | NS |
| *Streptococcus* spp. | 1 (5) | 0 | | | NS |

[a] Unless specified, all values are given as number (percent).
[b] NS, Not significant.
[c] Und, Undefined.

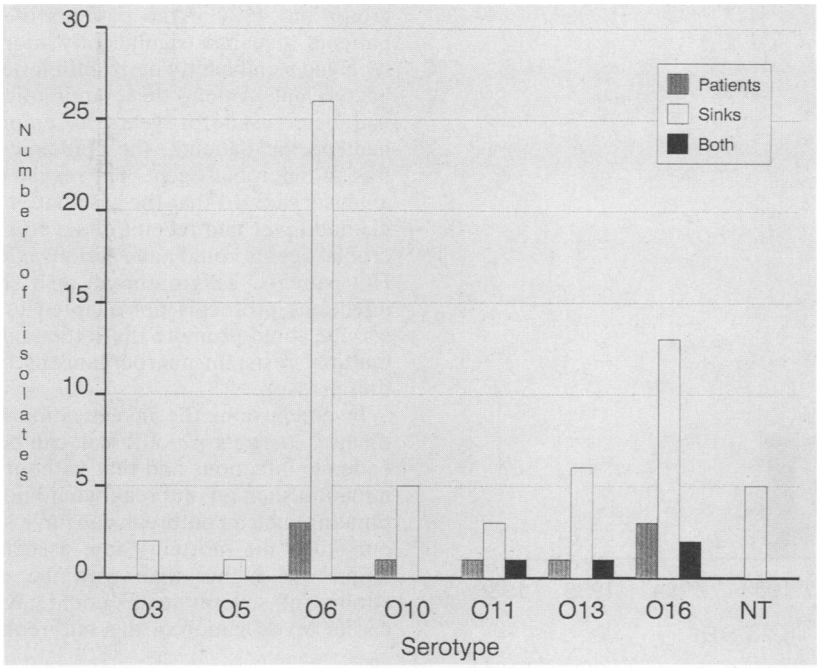


FIG. 1. Acquisition of *P. aeruginosa*; serotypes isolated from patients, sinks, or both.

cases, patient colonization preceded the isolation of the strain from the washbasin. The transmission of *P. aeruginosa* from washbasin drain to patient could not be documented.

**Control measures.** The contact isolation precautions from the Centers for Disease Control were used after 1 January 1983 for all patients infected or colonized with *P. aeruginosa*. In addition, the list of all HO patients who had at least one positive culture for *P. aeruginosa* serotype O16 was available in every nurse's station. If one of these patients was readmitted, he or she was placed in a private room and contact isolation precautions were instituted. At the same time, the use of ticarcillin as empiric therapy for febrile episodes in neutropenic patients was discontinued. There was a direct relationship between the institution of these policies and the reduction in the number of patients with *P. aeruginosa* O16 bacteremia (Fig. 2 and 3). The last case of bacteremia occurred in July 1983, and the strain has not been isolated at the hospital since July 1984.

## DISCUSSION

*P. aeruginosa* is the third most common cause of gram-negative sepsis, after *Escherichia coli* and *Klebsiella pneumoniae* (2). Although most *P. aeruginosa* infections are endemic, outbreaks have been described in different settings, such as surgical services (9), adult or pediatric intensive care units (4, 8), burn units (3, 7), and a neonatal nursery (6). To our knowledge, this is the first *P. aeruginosa* outbreak described in HO patients.

*P. aeruginosa* is the microorganism most frequently isolated from environmental sources such as sinks, handles, towels, racks, or bars of soap (7). Thus, the attention of physicians dealing with clusters of *P. aeruginosa* infection or colonization is often focused on the environment. In this outbreak, the epidemiologic investigation was delayed because the epidemic strain had been isolated from washbasin drains and several unsuccessful attempts were made to eradicate the strain with hypochlorite. Our epidemiologic investigation demonstrated that the reservoir for the epidemic strain was the colonized patients, not the environment. Several factors could have enhanced the transmission of the strain from colonized patients to other patients: the duration of the colonization; the site of colonization, such as the skin; and the failure of hospital personnel to adequately wash their hands or to place colonized or infected patients in contact isolation. Our prospective study of the acquisition of *P. aeruginosa* showed that *P. aeruginosa* serotype O16

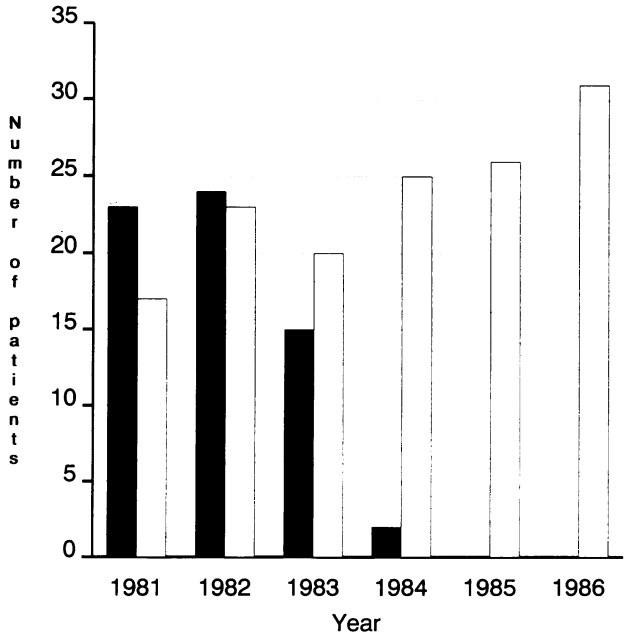


FIG. 2. Patients with *P. aeruginosa* bacteremia. Solid bar, Serotype O16; open bar, other serotypes.

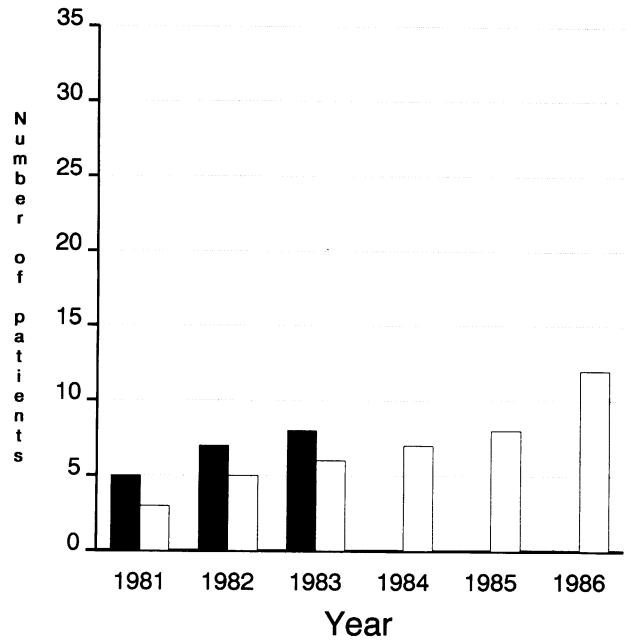


FIG. 3. Patients with *P. aeruginosa*-positive cultures. Solid bar, Serotype O16; open bar, other serotypes.

present in the sinks probably did not play a significant role in the transmission of the strain. This study confirms previous data showing that isolation of *P. aeruginosa* in the environment is a result of colonization of the patient, rather than its cause (5). The effectiveness of the isolation precautions used for patients colonized with *P. aeruginosa* O16 clearly demonstrates that colonized patients were the major reservoir for the epidemic strain.

To assess risk factors for *P. aeruginosa* serotype O16 bacteremia, we chose to use as a control group HO patients who developed *P. aeruginosa* bacteremia caused by serotypes other than O16. This choice was made because if we had randomly selected HO patients as a control group, we would have probably identified only some very broad risk factors for infection, such as neutropenia, that would not have been useful as predictors of *P. aeruginosa* O16 bacteremia. The other purpose of this case-control study was to try to understand why during the same period of time, among a relatively homogeneous population of HO patients, and in the same environment, some patients were infected with the epidemic strain and others were infected with endemic strains. The characteristics of control patients were similar to those described by Bodey et al. in their retrospective study of 410 episodes of *P. aeruginosa* bacteremia, while several risk factors were significantly associated with case patients (1). Case patients were characterized by the severity and the duration of their neutropenia; 81% had fewer than 100 granulocytes per $mm^3$, compared with 47% in the control group and 46% of the patients of Bodey et al. (1). Case patients also had significantly more days with fever and received significantly more antibiotics before the onset of the bacteremia. Among these antibiotics was ticarcillin, which had been used for years as empiric therapy for febrile neutropenic patients; the epidemic strain was resistant to this antimicrobial agent. The results of the logistic regression analysis showed that the association of prolonged neutropenia and fever and receipt of several broad-spectrum antimicrobial agents could have serious infectious consequences in HO patients. This outbreak also shows that empiric anti-infectious protocols not adapted to the ecology of an HO service could promote the settlement and the persistence of multiply resistant microorganisms because of strong selection pressure.

In conclusion, the investigation of this outbreak shows that a *P. aeruginosa* outbreak can occur at the same time as endemic infections and that without routine serotype determination such an outbreak would not be detected. Underestimating such an outbreak can have serious consequences: in our study the mortality rate associated with the epidemic strain was higher than with the endemic *P. aeruginosa* strains and several deaths could have been prevented by an earlier investigation of this outbreak.

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